With respect to the "additional sequences" recited in claim 134, this argument has been fully considered but is not persuasive for the same reasons as for claim 128 above. The "additional sequences" recited in the soluble fragment of claim 134 are identical to those found in the soluble fragment of claim 128.

B. The obviousness rejection of claims 62, 102, 103, 105-107, 110, 111, 113, 114, 119-121, 125-131 and 134-137 under 35 U.S.C. § 103 over Dembic et al (Cytokine 2: 231-237, 1990) in view of Capon (US Patent No. 5,116,964).

In this section of the Appeal Brief filed on 2/28/08, Appellants provide a "Brief Statement of Relevant Prosecution History" (pages 39-41) and then advance arguments why the rejection should be reversed (page 41-62). Appellants' statements regarding the prosecution history have been fully considered. No particular statements are disputed, but a response to the statement that, "[t]he Examiner did not explain why affinity purification compositions, which are not intended for administration to humans, would require sterile isotonic formulations" (page 40) is provided below in the section addressing the arguments against the rejection of the claims reciting "pharmaceutical compositions" (claims 114 and 137).

Appellants divide the arguments into eight sections by claim number. These arguments are addressed in the order presented in the Appeal Brief.

1. The obviousness rejection of claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130 (pg 41-55).

Appellants divide the arguments in this section into five parts (labeled "a" through "e"). These arguments are addressed in the order presented in the Appeal Brief.

a. Appellants' argument that the cited art teaches away from combining Capon with Dembic (pg 41-43).

Appellants argue that the teachings of *Capon* are primarily directed to providing molecules for *in vivo* administration. Appellants argue that soluble fragments of the 75 kD TNF receptor would be expected to have anti-inflammatory activity if administered,

and that Capon teaches that the immunoglobulin heavy chain constant region has pro-inflammatory activity that is retained by fusion proteins of such, and thus the skilled artisan would have been discouraged from combining the two elements for *in vivo* administration. Appellants further argue that the motivation to combine the elements based on affinity purification (as asserted in the rejection) "is not rational because affinity purification of TNF was already easily carried out with anti-TNF antibody" (page 42). Appellants argue (citing *KSR*) that obviousness rejections "cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness".

These arguments have been fully considered but are not found to be persuasive. As stated in MPEP 2123, "Patents are relevant as prior art for all that they contain" and "[t]he use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain" and "[a] reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments." The Examiner does not dispute that Capon teaches that the immunoglobulin heavy chain constant region has pro-inflammatory activity that is retained by fusion proteins of such, or that soluble fragments of TNFR could act as an anti-inflammatory agent. However, as set forth in the rejection, Capon also teaches that the hybrid immunoglobulins can be used for affinity purification of ligands (column 22, lines 5-6). This is a purely *in vitro* use for which an *in vivo* anti-inflammatory activity of the heavy chain constant region is not relevant. Furthermore, the ability to use antibodies to purify TNF does not negate the teachings of Capon regarding the use of binding agents fused to immunoglobulin heavy chain domains for ligand purification. The teachings of Capon present an alternative method of purification that adds to the existing knowledge base of the skilled artisan, rather than replacing it. As stated in MPEP 2123, "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments". Therefore, Appellants' arguments regarding the "rationality" of modifying Capon in view of Dembic are not found to be persuasive.

b. Appellants' argument that there was no motivation to select the claimed fusion proteins which are homodimeric (pg 43-44).

At pages 43-44, Appellants argue that there was no motivation to select the particular species of claimed fusion proteins (which are homodimeric) from the large genus of fusion proteins disclosed in Capon, including the large subgenus of homodimeric fusion proteins. Appellants argue that "[t]he selection of a species from a large genus disclosed in the prior art is nonobvious" and point to *In re Baird* (1994). Appellants argue that the skilled artisan would have expected a "monomeric form lacking disulfide bonding, such as TNFR-CH_2CH_3 fusion, to bind TNF with greater certainty of success" (page 44). Appellants argue that Capon teaches homodimeric fusion proteins in which the CH1 domain and a portion of the hinge region is deleted (in Example 5) and that contain the entire heavy chain constant region, whereas the claims are directed to a different species of fusion proteins that contains all of the domains of the constant region of an IgG heavy chain other than CH1.

These arguments have been fully considered but are not found to be persuasive. The instant specification does not provide a definition of the term "all of the domains of the constant region of an IgG heavy chain other than CH1". The specification does not teach whether the term "domains" includes the "hinge" as well as the CH1, CH2 or CH3 domains. Thus, the recitation of "all of the domains of the constant region of an IgG heavy chain other than CH1" broadly encompasses sequences that just contain the CH2 and CH3 domains. Furthermore, this recitation does not exclude domains that are present in a partial or mutated sequence. Thus, the claims broadly encompass fusion proteins in which all, none or a portion of the "hinge" is present. Capon specifically teaches, "Typically, such fusions retain at least functionally active hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain" (column 10, lines 10, 12). This shows that preferred embodiments informing the genus taught by Capon include those including each domain (CH2, CH3) of the constant region other than the first domain (CH1). With regard to the ability of a homodimeric species to bind TNF, Appellants refer to arguments in section "c"; therefore, these arguments are addressed

in detail below. However, in summary it is maintained that the skilled artisan would have had a reasonable expectation that a homodimeric fusion protein would bind TNF. Thus, it is maintained that the skilled artisan would have been motivated to select a homodimeric species from among the genus taught by Capon.

c. Appellants' argument that the assertion of reasonable expectation of success was based on uncorroborated factual assumption (pg 44-46).

At pages 44-46, Appellants argue that the assertion of reasonable expectation of success set forth in the rejection was based on an "uncorroborated factual assumption" that the claimed dimeric fusion proteins would bind trimeric TNF. Appellants argue that the Lesslauer Declaration A (page B-129 of the Appeal Brief) describes that there was uncertainty that the spatial configuration of the dimeric TNF receptor fusion protein would allow it to bind a trimeric TNF ligand. Appellants point to the statement at page 2 of the Declaration that "the spatial geometry of the receptor binding site was unknown. Thus, it could have been possible that the fusion with IgG fragments created a spatial structure that would have contained TNF receptor sequence but which, due to its spatial structure, was completely unable to bind TNFα". Appellants further dispute that Smith and Baglioni (1989; cited previously) provide evidence that the TNF trimer was known at the time of filing to bind a complex of two 75 kD receptor molecules. Appellants argue that none of sequences in Smith and Baglioni have been shown to contain the particular sequences recited in the pending claims.

These arguments have been fully considered but are not found to be persuasive. It is conceded, as pointed out by Appellants, that Smith and Baglioni (1989) do not clarify specific receptor subunits found in the multimeric complexes, particularly in view of the later findings that two distinct receptor sequences exist (i.e., the 55 kD and 75 kD TNFRs). It is therefore conceded that this argument successfully weakens Smith and Baglioni as evidence in support of a reasonable expectation of success. However, the rejection is maintained for the following reasons.

First, *KSR Int'l. Co. v. Teleflex Inc.* (2007) states "if a person of ordinary skill artisan can implement a predictable variation, § 103 likely bars its patentability. For the

same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill" reasonable expectation of success. Thus, in view of *KSR* an obviousness rejection under U.S.C. § 103 does not actually require a test of a "reasonable expectation of success". In the instant case, the use of a soluble TNF receptor as a "ligand binding partner" in the invention of Capon is a predictable variation. The skilled artisan would recognize would that the immunoglobulin fusion would predictably improve a soluble TNF receptor (for use in purification of its ligand) in the same manner as Capon teaches generally for other ligand binding partners (e.g., extracellular domains of receptors).

Second, the statement in the Lesslauer Declaration merely suggests a possibility (i.e., that it "could have been possible" the fusion protein would not bind TNFα), and does not provide any evidence that the skilled artisan would have had a greater expectation that it would not bind than an expectation that it would bind. The corollary of the statement in the Declaration is that it "could have been possible" that the fusion protein would have been able to bind TNFα. The Declaration does not provide any indication or evidence as to which of these possibilities would have been held to be more likely to prevail. The Declaration provides no evidence showing why an IgG fusion would predictably create a geometry that would prevent binding. Furthermore, the skilled artisan would have also considered the binding possibilities in view of the teachings of Dembic (1990). Specifically, Dembic also teaches a TNF-binding soluble fragment of the 75kD human TNF receptor that contains sequences that are presumably from the extracellular region (pg 235, left column). This molecule has a different tertiary structure from the full-length receptor yet can bind to TNF. Thus Dembic provides evidence that the C-terminal domain of TNFR2 is not critical to the binding of TNF. Thus, the evidence set forth in the Lesslauer Declaration and the reference of Dembic has been fully considered, and the preponderance of the evidence supports that the skilled artisan would have predicted that the C-terminal sequences of TNFR2 could be replaced without altering binding.

Third, even if the skilled artisan would have predicted a dimeric TNFR-immunoglobulin dimeric to not be able to bind, the teachings of Capon provide an additional motivation to combine the teachings of Dembic in view of Capon - to construct a monomeric version of the fusion protein encompassed by claims. Appellants argue that the claimed protein is "dimeric", yet this limitation is not recited in the claims or even taught by the specification. Instead, as set forth above, the recitation of "all of the domains of the constant region of an IgG heavy chain other than CH1" broadly encompasses sequences that contain just the CH2 and CH3 domains and thus encompass fusion proteins in which all, none or a portion of the "hinge" is present.

Capon teaches that "in some embodiments the hybrid immunoglobulins are assembled in monomers..." (column 10, lines 27-28). Capon shows a typical monomer structure comprising heavy chain domains (column 10, line 61). Capon also teaches that two cysteine residues of the hinge are responsible for immunoglobulin dimerization (column 40, lines 46-48). Thus, it would have also been obvious to the skilled artisan at the time the invention was made to fuse the extracellular portion of the TNF receptor sequence taught by Dembic to a monomeric region taught by Capon, and to recombinantly produce the protein in CHO cells and purify the protein produced as taught by Capon. The person of ordinary skill in the art would be motivated to do so for the same reasons as with a dimeric immunoglobulin sequence - to produce and purify the TNF receptor-Ig fusion for use in affinity purification of the TNF ligand. The person of ordinary skill in the art would have expected success because Capon teaches that immunoglobulin fusions can be made with a wide variety of proteins, and teaches all of the techniques for recombinant production of hybrid immunoglobulins in CHO cells and purification of the produced protein. Thus, the level of skill in the art at the time of filing is such that even if the skilled artisan would have predicted the dimeric form to lack TNF binding functionality, the skilled artisan could have predictably created a monomeric form encompassed by the claims.

Fourth, Capon also provides an additional motivation for constructing either the dimeric or monomeric TNFR2-immunoglobulin fusion proteins irrespective of whether the fusion protein itself can bind to TNF. Specifically, Capon also teaches that "The

novel polypeptide of this invention are useful in diagnostics or in purification of the ligand binding partner by immunoaffinity techniques known per se. Alternatively, in the purification of the binding partner, the novel polypeptides are used to adsorb the fusion from impure admixtures, after which the fusion is eluted and, if desired, the binding partner is recovered from the fusion, e.g., by enzymatic cleavage" (column 17, lines 54-61). Capon teaches that "[l]igand binding partners as defined herein are proteins known to function to bind specifically to target ligand molecules, and are generally found in their native state as secreted or membrane bound polypeptides..." (column 7, lines 13-16). Thus, Capon also teaches immunoglobulin fusion proteins for use in production and purification of the "ligand binding partner" joined to the immunoglobulin domains. Thus, the skilled artisan would also have been motivated to construct the claimed protein solely for production and purification of the extracellular region of the TNF receptor taught by Dembic (which is a membrane bound protein). According to the teachings of Capon, the ligand binding partner is recovered from the fusion after production, for example by cleavage. Thus, the skilled artisan would have recognized that the immunoglobulin portion of the protein is removed and thus would not impact the ability of the ligand binding partner to bind its ligand. Thus, even if the skilled artisan would have predicted a dimeric TNF receptor-immunoglobulin fusion to lack TNF binding functionality, the skilled artisan would have still have been motivated by Capon to create such a fusion for purification of the ligand binding partner (e.g., TNF receptor extracellular domain).

d. Appellants' argument that the Examiner legally erred in refusing to evaluate the evidence of unexpected results (pg 47).

At page 47, Appellants argue that the Examiner legally erred in refusing to evaluate the evidence of unexpected results. Appellants argue that the "Examiner provided no other comments on the merits of the evidence or any indication that he evaluated the evidence at all" (page 47). Appellants argue that the Examiner must consider all evidence when assessing patentability.

These arguments have been fully considered but are not found to be persuasive. Contrary to Appellants' assertion, the Examiner did provide meaningful consideration of Appellants' evidence. As set forth in MPEP 2145, the Examiner "set forth the facts and reasoning that justify" the conclusion that "the evidence is insufficient to rebut the *prima facie* case of obviousness". This reasoning was as follows.

At page 18 of the 2/23/07 Office Action (Final Rejection), the Examiner stated that "[t]he evidence of unexpected results presented by Appellants is not sufficient to overcome the rejection. Appellants' putative unexpected results appear to be generated using a fusion protein comprising the full-length extracellular domain of the insoluble 75 kD TNF binding receptor and portions of an immunoglobulin molecule. However, as set forth above, in the section "Claim Rejections - 35 U.S.C. 112, 1st paragraph, written description", the specification does not provide a description of this particular species of fusion protein. There is no conception in the specification at the time of filing of this particular species of fusion protein. Therefore, the evidence of unexpected results found with this particular species of receptor-Ig fusion is not sufficient to overcome the obviousness of combining the teachings of Dembic in view of Capon."

Thus, the Examiner did indicate that Appellants' results with the particular species were fully considered, and further acknowledged that they did constitute unexpected results, but did not find this evidence of unexpected results sufficient to overcome the rejection. MPEP 2145 states, "a showing of unexpected results for a single member of a claimed subgenus, or a narrow portion of a claimed range would be sufficient to rebut a prima facie case of obviousness if a skilled artisan "could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof." In the instant case, Appellants have submitted evidence of unexpected results with a single species (a fusion comprising a full-length extracellular domain of a 75 kD human TNF receptor) of a claimed genus (a fusion comprising any "soluble fragment" of 75 kD human TNF receptor). However, as set forth in the written description rejection, the specification as originally filed does not provide any teachings pointing to this particular species, and in fact teaches away from this species by repeatedly referring to TNF-binding fragments of the sequence of Figure 4 (SEQ ID NO:

4). If amended claims were submitted in the instant application that were directed to a protein comprising a soluble fragment specifically identified as the full-length extracellular domain of a 75 kD TNF receptor, they would be rejected for containing new matter. The specific use of the entirety of the extracellular domain represents a teaching that goes beyond the original disclosure. Furthermore, the prior art teaches (Chan, 2000) that the fragments of SEQ ID NO: 4 would not have been able to bind to TNF. For these reasons, the skilled artisan could not ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof. Furthermore, Appellants do not provide any evidence that the unexpected results extend to the full range of the claimed genus of "soluble fragments" of part (a) of each claim, including mutated variants of a 75 kD insoluble TNF receptor.

e. Appellants' arguments regarding unexpected results (pg 48-54).

At pages 48-54, Appellants provide a description of the unexpected results found with a species encompassed by the claims, including (i) unexpectedly absent or drastically reduced pro-inflammatory effector functions (pages 49-51); (ii) lack of aggregating ability (pages 51-53); (iii) unexpected thousand-fold increased potency in TNF neutralizing activity (page 53); and (iv) unexpectedly increased binding affinity and kinetic stability (page 54).

(i) At pages 49-51, Appellants describe how a fusion protein consisting of "the extracellular domain of p75 TNFR fused to all of the domains of an IgG1 heavy chain constant region other than CH1" had "drastically reduced, if not completely eliminated, effector function as compared to an anti-TNF antibody". Appellants argue that this result is unexpected in view of the teachings of the art, including Capon (used in the rejection), which teaches that its hybrid immunoglobulin fusion proteins were expected to retain immunoglobulin effector functions.

Appellants' arguments have been fully considered but are not sufficient to overcome the rejection. The Examiner does not dispute that the drastically reduced effector function observed for a fusion protein consisting of "the extracellular domain of p75 TNFR fused to all of the domains of an IgG1 heavy chain constant region other

than CH1" was an unexpected result. However, as stated above, there is no conception in the specification at the time of filing of the particular species of fusion protein containing the full-length extracellular domain of the 75 kD human TNF receptor. Therefore, the evidence of unexpected results found with this particular species is not sufficient to overcome the obviousness of combining the teachings of Dembic in view of Capon.

(ii) At pages 51-53, Appellants describe how a fusion protein consisting of "etanercept" (citing the same reference as in section (i) above) failed to form "high molecular aggregates when combined with TNF" as observed with two different anti-TNF antibodies. Appellants argue that this result is unexpected in view of the presence of an Fc region in the fusion protein which the skilled artisan would have predicted to "form aggregated complexes with trimeric TNF ligand" (page 52).

Appellants' arguments have been fully considered but are not sufficient to overcome the rejection. The Examiner does not dispute that the failure of a fusion protein consisting of "the extracellular domain of p75 TNFR fused to all of the domains of an IgG1 heavy chain constant region other than CH1" to form aggregating complexes was an unexpected result. However, as stated above, there is no conception in the specification at the time of filing of the particular species of fusion protein containing the full-length extracellular domain of the 75 kD human TNF receptor. Therefore, the evidence of unexpected results found with this particular species is not sufficient to overcome the obviousness of combining the teachings of Dembic in view of Capon.

(iii) At page 53, Appellants describe how a fusion protein consisting of a "soluble p75 TNFR fusion protein within the scope of the claims" had "an unexpected 50-fold improvement in TNF neutralizing potency in *in vitro* biological activity assays, compared to the unfused, soluble p75 TNFR". The evidence is provided from the publication of Mohler (1993; page B-181 of the Appeal Brief). Appellants argue that this result is unexpected in view of the teachings of the art such as Capon, which teaches "no such increase in potency" for other "immunoglobulin fragment fusions such as CD4-IgG".

Appellants' arguments have been fully considered but are not sufficient to overcome the rejection. Mohler does not describe the exact sequence of the

extracellular domain of the 75 kD human TNF receptor used in immunoglobulin fusion. However, Figure 1 of Mohler (page 1550) shows that the extracellular domain of the fusion does include all four domains of said TNF receptor. Dembic (1990) teaches that the first domain consists of residues 17-54 of the receptor (see Figure 2 on page 233 of Dembic, 1990). The instant specification does not teach use of a soluble fragment comprising these residues. In particular the protein sequence of Figure 4 (SEQ ID NO: 4) consists only of residues 49-439 of the full-length receptor taught by Dembic, and thus any fragment of this receptor would not include residues 17-49 of the sequence used by Mohler. Furthermore, the post-filing date art (Chan, 2000) provides evidence that a region consists of amino acids 10-54 is required for TNF binding. Thus, while the Examiner does not dispute that the increase in TNF neutralizing potency observed by Mohler was an unexpected result, there is no conception in the instant specification at the time of filing of the particular species of fusion protein containing the full-length extracellular domain of the 75 kD human TNF receptor as used by Mohler. Therefore, the evidence of unexpected results found with this particular species is not sufficient to overcome the obviousness of combining the teachings of Dembic in view of Capon.

(iv) At page 54, Appellants refer to results described in Lesslauer Declaration A (Appendix B-129 of the Appeal Brief). The Declaration describes a fusion protein consisting of "the soluble extracellular domain of the 75 kD TNF receptor" and "the heavy chain of a human IgG3 molecule which is missing the CH1 domain and contains the hinge, CH2 and CH3 domains". The Declaration includes results showing that this fusion protein had "an excellent binding activity". The Declaration also states that the fusion protein had "an unexpectedly higher kinetic stability" and "a surprisingly improved inhibition of the effect of TNF in biological cell culture tests"; the results leading to these conclusions are shown in comparison to results observed for the isolated soluble extracellular domain. Appellants argue that these results are unexpected in view of the teachings of Capon (cited in the rejection) teaching that a CD4/IgG fusion bound to its ligand with the same kinetic stability as the soluble, unfused CD4.

Appellants' arguments have been fully considered but are not sufficient to overcome the rejection. First, the Examiner disputes that the "excellent binding activity"

was an unexpected result. The Declaration does define "excellent binding activity" or distinguish this term from "binding activity" in general. For the reasons set forth above in section "c", the skilled artisan would have predicted that a fusion of the extracellular domain of the 75 kD TNF receptor with dimeric immunoglobulin sequences would be able to bind to TNF. Furthermore, the Figure on page B-138 does not show any difference in the initial binding activity between the fusion protein and a soluble extracellular domain. Second, it is not disputed that the "kinetic stability" and "improved inhibition of TNF" observed for a fusion protein consisting of "the soluble extracellular domain of the 75 kD TNF receptor" and "heavy chain of a human IgG3 molecule which is missing the CH1 domain and contains the hinge, CH2 and CH3 domains" was an unexpected result. However, as stated above, there is no conception in the specification at the time of filing of the particular species of fusion protein containing the full-length extracellular domain of the 75 kD human TNF receptor. Therefore, the evidence of unexpected results with this particular species is not sufficient to overcome the obviousness of modifying the teachings of Dembic in view of Capon.

2. The obviousness rejection of claims 105 and 113 (pg 55-56).

In this section, Appellants advance the same arguments as for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130 (as in sections 1a-1e above). Appellants further argue that the claims are limit to immunoglobulin IgG_1 isotype and that the evidence shows unexpected results with respect to improved TNF binding and neutralization for both IgG_1 and IgG_3 isotypes and additional unexpected results with respect to reduction of effector function and absence of aggregation ability for IgG_1.

These arguments have been fully considered but are not found to be persuasive. The repeated arguments have been fully considered, but are maintained for the same reasons set forth above for claims 62, 102, 103, 107, 110, 111, 119, 120, 129 and 130. With respect to the IgG isotype recited in these claims (IgG_1), Capon specifically teaches use of this isotype, as set forth in the rejection (Capon teaches IgG_1 in column 14, line 66). Therefore, Appellants' unexpected results with respect to this isotype is not